Supplement 1: Multiple Product Models of Population Health Effects for Cigarettes and Other Tobacco Products

There are no models that specifically consider the health impact of IQOS, but several simulation models analyze the impact of two tobacco products on population health: cigarettes and e-cigarettes;[1-5] cigarettes and a generic MRTP (or reduced risk tobacco product),[6-9] and cigarettes and snus.[10] The models, the assumptions they are based on, and the findings are summarized here. Only models that include a measure of population health as an outcome (e.g. mortality) and include estimates for the US are reviewed. Included are models developed by independent researchers[1-5] and those employed by or funded by the tobacco industry.[6 8 9 11]

Cigarettes and e-cigarettes

Kalkhoran and Glantz[1] developed a Monte Carlo model that was used to predict steady state population health effects in the US and the UK, allowing for e-cigarette impacts on youth initiation as well as adult cessation. Tobacco-related health effects were measured using an index, ranging from 100 for a current cigarette smoker to 0 for a never tobacco user.[10] The relative harm of e-cigarettes compared to cigarettes was varied from 1-50% as harmful. They concluded that the net impact on population health would be negative if e-cigarettes are more than 20-30% as harmful as cigarettes. Levy and colleagues,[2] assuming that e-cigarettes are 5-25% as harmful as cigarettes and that e-cigarette use leads to little change in cigarette initiation rates, concluded that e-cigarettes are likely to have a positive impact on reduced smoking-attributable deaths and life years lost, unless e-cigarette prevalence becomes very high. They used the model to predict the impact of e-cigarette use replacing cigarette smoking.[3] With the excess risk of e-cigarettes vs. cigarettes ranging from 5-10% and assuming that 5-10% of the population continue to smoke, they concluded that there would be a substantial reduction in mortality by 2100. Soneji and colleagues[4] used a Monte Carlo stochastic simulation model to look at mortality effects of e-cigarette use considering the impact on smoking initiation among never smoking youth and young adults as well as the impact on smoking cessation among adult current smokers. They found that e-cigarette use resulted in net population harm, because the number of adults who quit smoking would be greatly exceeded by the number of never-smoking adolescents and young adults who would initiate cigarette smoking, even though e-cigarettes were assumed to be 5% as harmful than cigarettes. Warner and Mendez[5] used a dynamic simulation model that they have developed and refined over more than 2 decades to track adult smoking status and mortality to 2070 in the presence of e-cigarettes. In contrast to Soneji, they found that smoking cessation resulting from e-cigarette use more than compensated for increased smoking initiation in scenarios in which smoking initiation increased between 2-6% and smoking cessation increased between 6-10%.

Cigarettes and a nonspecified MRTP

Bachand and Sulsky[6] modeled all-cause mortality for a hypothetical cohort after the introduction of a MRTP. Using switching rates of 2-10% from cigarettes to the MRTP, 5-50% MRTP initiation rates among never smokers, 20% of MRTP initiators switching to cigarettes, and assuming the MRTP mortality risk was 5-11% that of cigarettes, they concluded that the new MRTP product would reduce mortality. Vugrin and colleagues[7] developed a multi-state dynamical systems model and concluded that the benefits of switching to a reduced risk product can be offset by increased initiation rates of the product. They report that mortality would increase if the new product is 50% as risky as cigarettes and 50% of initiates are never smokers. Poland and Teischinger[11] analyzed excess mortality after the introduction of a MRTP incorporating a decline of excess risk of cigarette smoking over time after quitting smoking or smoking fewer cigarettes. They found a reduction in mortality when assuming that dual

MRTP/cigarette users smoke fewer cigarettes per day than sole smokers, and that 25% of smokers would use the MRTP instead of cigarettes as would 5% of never-smokers and 0.5% of former smokers. They assumed that the MRTP had only 4% the mortality risk of cigarettes.

Cigarettes and snus

Mejia and colleagues[10] evaluated the impact of promoting use of the smokeless product snus as a harm reduction strategy. The authors developed the health index used by Kalkhoran and Glantz.[1] They concluded that promoting snus as a safer product than cigarettes is not likely to result in population health benefits.

The difference in findings among the models is largely a result of the assumptions incorporated into the analyses, including health risks of the MRTP and of dual use compared to cigarettes, changes in cigarette smoking initiation rates of youth and nonsmokers due MRTP use, and changes in cigarette smoking cessation rates for adults due to MRTP use. Studies that assumed the MRTP was much less risky than cigarettes (in the range of 0 to 50%), assumed low MRTP initiation rates of never-smoking youth, and assumed high rates of cigarette smoking cessation among MRTP users, were likely to find a population health benefit from the introduction of a new MRTP.

Supplement 2. The Philip Morris International (PMI) Population Health Impact Model (PHIM)

PMI researchers and their collaborators developed the PHIM to examine the impact on mortality of introducing a MRTP. For the IQOS MRTP application, the model was extended to allow for dual use of the new product and cigarettes. This modified model was then documented in a publication that focused on the effect of varying assumptions on mortality.[9]

The PHIM consists of two components, the prevalence component ("P-component") and the epidemiological risk component ("E-component").[8] "The P-component is a Markov chain state-transition model to estimate changes in the distribution of conventional cigarettes and/or MRTP use occurring in a hypothetical population of a given size over a defined period, separately for the Null and MRTP Scenarios"[8] (p. 88). For each scenario, transition probabilities from never or former smokers to current cigarette or MRTP use, from current cigarette or MRTP use to quitting, and for switching products, are estimated from actual cigarette smoking prevalence data for 1986 and later from 12 countries including the US, and "assumptions and product use patterns from controlled studies that cannot be validated with regard to post-market actual use" are used for estimating the MRTP use.[8] The E-component uses the tobacco use patterns from the P-component along with estimates of the RR of death for four diseases: lung cancer, ischemic heart disease (IHD), stroke, and chronic obstructive pulmonary disease (COPD) to estimate mortality.

The RR of death from smoking is based on published findings. The PHIM assumes that the RR of death from IQOS is a fraction of the RR of death from cigarette smoking. The authors rely on a measure called "the relative exposure of IQOS compared to smoking cigarettes", denoted by "f"[12] (page 19, 22-23). The mean value of "f" is estimated at 0.35 and the median value is 0.30, but f-values between 0.1 and 0.3 are used in simulations. The RR of mortality caused by the four smoking-related diseases that were used to estimate f-value in the PHIM were obtained from studies conducted by British researchers at a private consulting firm funded by PMI,[13-16] and estimates from a published meta-analysis[17] involving 39 North American studies[12] (page 28). The RR of death for cigarette smoking for each disease is multiplied by the f-value (0.1 to 0.3), so the RR of death from IQOS use is 70 to 90% lower than the RR from cigarette smoking.

Supplement Table 1. Multiple Product Models of Population Health Effects for Cigarettes and Other Tobacco Products				
Products	**Citation**	**Model Description**	**Assumptions**	**Findings**
Cigarettes and e-cigarettes	Kalkhoran and Glantz, 2015[1]	"A base case model was developed using data on actual cigarette and e-cigarette use patterns that quantifies transitions from an initial state of no cigarette or e-cigarette use to 1 of 5 final states" (never cigarette use, never e-cigarette use, cigarette use, e-cigarette use, dual use, or quit). Changes in net health effects were modeled under 7 scenarios that varied use patterns and RR of e-cigarette use using Monte Carlo simulation for the US and UK populations for a steady state. Health impacts were measured on a unitless scale, ranging from 100 for a current cigarette smoker to 0 for a never tobacco user.	E-cigarette risks from 1-50% as harmful as cigarettes were considered. Different scenarios vary whether e-cigarettes are used by smokers who want to quit or not, by youth who would or would not have otherwise smoked cigarettes, smoking cessation rates, e-cigarette initiation rates, and the health risk of e-cigarettes compared to cigarettes.	The overall population health effect of e-cigarette use would be positive if e-cigarettes are not very dangerous and negative if they are more than 20-30% as dangerous as cigarettes. Net benefits would be positive if e-cigarettes are used only by smokers who want to quit or youth who would have smoked cigarettes. Net benefits are negative if e-cigarette use results in renormalization of cigarette use or are used by youth who would not have otherwise smoked.
Cigarettes and vaporized nicotine products - VNP (e.g. e-cigarettes)	Levy et al., 2017[2]	"The public health impact of vaporized nicotine product use are modeled in terms of how it alters smoking patterns among those who would have otherwise smoked cigarettes and among those who would not have otherwise smoked cigarettes in the absence of VNPs. The model incorporates transitions from trial to established VNP use, transitions to exclusive VNP and dual use, and the effects of cessation at later ages." The model follows a cohort of 15-year olds in 2012 through 2083 and analyzes the impact on smoking-attributable deaths and life-years lost.	Model considers e-cigarettes to be 5-25% as harmful as cigarettes. Model assumes odds of cigarette initiation was only slightly greater for ever e-cigarette users than never e-cigarette users (OR=1.16)	"Under most plausible scenarios, VNP use generally has a positive public health impact. However, very high VNP use rates could result in net harms."

Cigarettes and e-cigarettes	Levy et al., 2018[3]	The model projects cigarette use by the US population aged 15-99 in 2016 through 2100. The model projects smoking-attributable deaths using age- and sex-specific initiation and cessation rates and age- sex- and smoking status-specific mortality rates.	Status quo scenario: assumes no e-cigarette use and projected smoking initiation and cessation rates. Optimistic scenario: e-cigarettes have 5% the excess risk of smoking, 5% of the population initiates smoking or remains smokers. Pessimistic scenario: e-cigarettes have 10% the excess risk of smoking, 10% of the population initiates smoking or remains smokers.	If vaping largely replaced smoking, 20.8-86.7 million life-years lost (1.6-6.6 million deaths) would be avoided by 2100, depending on the scenario.
Cigarettes and e-cigarettes	Soneji et al, 2018[4]	"Monte Carlo stochastic simulation model. Model parameters were drawn from census counts, national health and tobacco use surveys, and published literature. We calculate the expected years of life gained or lost from the impact of e-cigarette use on smoking cessation among current smokers and transition to long-term cigarette smoking among never smokers for the 2014 US population cohort."	The base case used smoking and e-cigarette prevalence, initiation, and quit rates for adolescents and adults from national data and published studies. Assumed e-cigarettes were 5% as harmful as cigarettes. Sensitivity analyses varied initiation, cessation, and e-cigarette prevalence rates, and varied relative harm from e-cigarettes from 0-100%.	"Based on the existing scientific evidence related to e-cigarettes and optimistic assumptions about the relative harm of e-cigarette use compared to cigarette smoking, e-cigarette use currently represents more population-level harm than benefit." Found net negative impact even assuming e-cigarettes are 95% less harmful than cigarettes.
Cigarettes and e-cigarettes	Warner and Mendez, 2018[5]	"…dynamic model that tracks the US adult population's smoking status and smoking-related deaths over time" was used to "simulate the effects of vaping-induced smoking initiation and cessation on life-years saved or lost to the year 2070." Data from census (population distribution), NHIS (smoking prevalence), death rates (Statistical Abstracts of the US, CPS II)	Base case: 2% increase in smoking initiation, 10% increase in smoking cessation; "worst case": 6% increase in initiation, 5% increase in smoking cessation. Considers mortality from smoking cigarettes only in base case; sensitivity analysis considers e-cigarettes 10% as risky as cigarettes.	"Potential life-years gained as a result of vaping-induced smoking cessation are projected to exceed potential life-years lost due to vaping-induced smoking initiation… …over a wide range of plausible parameters."
Cigarette and MRTP	Bachand and Sulsky, 2013[6]*	Dynamic Markov Chain Monte Carlo population model to estimate all-cause mortality for hypothetical cohort who switch from cigarette smoking to the use of a MRTP	Analyzed rates of switching from cigarettes to MRTP of 2-10% and MRTP initiation rates for never smokers of 5-50%. The MRTP product was considered to have a mortality risk of .05-.11 times that of cigarettes	Concluded that switching from cigarette smoking to an MRTP was more likely to produce population health benefits than initiation with an MRTP

Cigarettes and a lower risk tobacco product	Vugrin et al., 2015[7]	"...a multi-state, dynamical systems population structure model that can be used to assess the effects of tobacco product use behaviors on population health. The model incorporates transition behaviors, such as initiation, cessation, switching, and dual use, related to the use of multiple products. The model tracks product use prevalence and mortality attributable to tobacco use..."	Base case: new product is 25% as risky as cigarettes, 1.5% of cigarette smokers switch to new product each year, 1.5% become dual users each year,25% of switchers/dual users would have otherwise quit, 50% of new initiates would have otherwise been cigarette smokers, 5% of new product users switch to cigarettes and 5% switch to dual use each year. Sensitivity analysis considered a scenario where 1% of smokers switch to the new product and 2% of smokers become dual users each year.	"We demonstrate that potential benefits from cigarette smokers switching to the lower-risk product can be offset over time through increased initiation of this product. Model results show that population health benefits are particularly sensitive to product risks and initiation, switching, and dual use behaviors." Increases in deaths result if the new product is 50% as risky as cigarettes and 50% of never smokers initiate use

Cigarettes and MRTP	Weitkunat et al., 2015[8]*	"...Philip Morris International (PMI) has developed a Public Health Impact Model (PHIM) to estimate the reduction in the number of deaths over a period following the introduction of an Modified Risk Tobacco Product (MRTP)… …The model is based on publicly available data on smoking prevalence and on the relationships between smoking-related disease-specific mortality and various aspects of the smoking of conventional cigarettes (CCs), together with an estimate of exposure from the MRTP relative to that from CCs..." The prevalence component of the model is a Markov chain state-transition model which estimates changes in use of CCs and MRTP for a null and MRTP scenario. Model does not allow for dual use of CCs and MRTP. Smoking transition probabilities (STPs) from never or former smokers to current CC or MRTP use, current CC or MRTP users quitting, or switching products, are estimated from actual CC data and "assumptions and product use patterns from controlled studies that cannot be validated with regard to post-market actual use" for MRTP. The epidemiologic risk component of the model uses the prevalence results to estimate mortality from lung cancer, IHD, stroke, and COPD.RR (RR) of death from CC use is based on published findings. RR of death from MRTP is based on assumptions about how much less risky the MRTP is compared to cigarettes.	Model is described in theory, but not used for estimates. "If the "effective dose" is taken as 1 unit when smoking CCs, and as 0 units when not smoking, then the effective dose when using the MRTP is taken as F units (assumed to be <1). The smaller is F, the smaller the excess risk (ER) associated with use of the MRTP, and the closer the ER associated with switching from CCs to the MRTP becomes to zero, the ER associated with smoking cessation." The value for F is derived based on aerosol chemistry data, toxicology assessments, pharmacokinetic and smoking topography data, analysis of blood and urinary biomarkers of exposure, measurements of functional and subjective health. "Methods of aggregating these data are being developed to estimate the likely probability density of F considering the integrated available empirical evidence."	Paper discusses the model, but does not report specific findings.

Cigarettes and a reduced risk tobacco product	Lee et al., 2017[9]*	"We use Population Health Impact Modelling to assess effects on tobacco prevalence and mortality of introducing a Reduced Risk Tobacco Product (RRP). Simulated samples start in 1990 with US-representative smoking prevalence. Individual tobacco histories are updated annually until 2010 using estimated probabilities of switching between never-current/former smoking where the RRP is not introduced, with current users subdivided into cigarette/RRP/dual users where it is. RRP-related mortality reductions from lung cancer, IHD, stroke, and COPD are derived from the histories and the assumed RRs of the RRP".	Base case assumes that the RRP reduces "dose" by 80% in users and 40% in dual users. Assumes uptake of 10% for the RRP and 6% for dual users after 10 years.	Mortality reduction is proportional to the dose reduction. "Plausible increases in re-initiation or dual users' consumption, or decreased quitting by smokers would not eliminate the drop."
Cigarette and MRTP	Poland and Teischinger, 2017[11]*	"A Monte Carlo simulation model generates random individual product use histories, including cigarettes smoked per day (CPD), to project cumulative deaths through 2060 in a population with versus without the MRTP. Transitions are modeled to and from dual use, which affects CPD and cigarette quit rates, and to MRTP use only." Model takes into account exponential decay of excess risk over time.	Assumes dual users of MRTP and cigarettes smoke fewer cigarettes per day than those who only smoke cigarettes. Assumes 25% of would-be cigarette smokers will use MRTP instead, and 5% of would-be non-smokers as well as .5% of former smokers will use MRTP. Assumes excess risk of mortality from MRTP use is 4% of risk from cigarettes.	"Results in a hypothetical scenario showed high sensitivity of long-run mortality to CPD reduction levels and moderate sensitivity to excess risk transition rates." "Data on relative mortality risk versus CPD suggest that this reduction may have a substantial effect on mortality rates, unaccounted for in other models."
Cigarettes and snus	Mejia, Ling, and Glantz, 2010[10]	"A Monte Carlo simulation of a decision tree model of tobacco initiation and use was used to estimate the health effects associated with five different patterns of increased smokeless tobacco use" to evaluate whether snus should be promoted as part of a harm reduction strategy. Health impacts were measured on a unitless scale, ranging from 100 for a current cigarette smoker to 0 for a never tobacco user.	Transition probabilities from cigarette or smokeless initiation to cessation, cigarette smoking, smokeless use, or dual use are analyzed under 4 circumstances: stable smoking (smokers don't consider quitting), health-concerned smokers, smokers in smokefree environments, and smokers who are price sensitive.	Authors concluded that decreased cigarette use and increased snus use are unlikely to result in reduced population harm.

*Research conducted and/or funded by tobacco industry

Supplement Table 2. PHIM Treatment of Impact of IQOS on 7 Population Groups and Exposure Patterns Recommended by the FDA for Consideration	
Group	**Description in PMI MRTP Application**
1) Tobacco users who switch from other products to the proposed product	"The Prevalence Component only accounts for the use of cigarettes and an MRTP, and does not consider other tobacco products, such as cigars, pipes or smokeless tobacco. Failure to do so might cause some bias in estimating the reduction in deaths attributable to an MRTP if CC smokers switching to an MRTP tend to change their use of these other products. However, unless evidence emerges that this occurs to any material extent, no attempt will be made to account for this possibility, as this would make the estimation process extremely complex and highly unreliable due to the number of assumptions required and the interactions between the smoking statuses."[12] (Module 6, p. 7) "Ignoring e-cigarettes may also not have a big impact on the model outcomes if claims that any health effects are less than 5% of those from cigarettes are correct... ..However, if the prevalence of the use of e-cigarettes continues to increase, it will be important to expand the model to account for this tobacco use behavior."[12] (Module 6, page 41)
2) Users of the new product who then switch to other products with greater health risk	PMI states that this "relates to switching from MRTPs to conventional cigarette"[13] (Module 7.4, page 5).
3) Tobacco users who use the new product rather than quit tobacco use	PMI indicates that this group was "considered by a specific analysis in which current conventional cigarette smokers who would otherwise have switched to MRTP or to dual use, quit instead"[18] (Module 7.4, page 5). PMI indicates that "here, the reduction in deaths associated with MRTP introduction was estimated to be about 11 times greater in males and about 13 times greater in females than that for the basic analysis"[18] (Module 7.4, page 5).
4) Tobacco users who use the new product rather than FDA-approved tobacco cessation medication	This is not considered in the PHIM because they consider it to be "outside the present scope of the model" [13] (Module 7.4, page 5).
5) Non-users who initiate tobacco use with the new product, including youth, never users, and former users	The model includes transition rates between former smoking, never smoking, and IQOS use
6) Users who use the new product as well as other tobacco products	The model includes transition rates between current, former, and never smoking and IQOS use, and dual IQOS/cigarette use.
7) Non-users who experience health risks from the product	Risk to non-users is ignored because PMI argues that this is "outside the present scope of the model"[18] (Module 7.4, page 5). PMI further states that "When estimating the reduction in the number of deaths associated with the introduction of THS, the PHIM does not account for ETS exposure. Recent meta-analyses on ETS and lung cancer,[19] COPD,[20] IHD,[21] and stroke[22] show that, for these diseases, the RRs associated with ETS exposure in never smokers is much lower than the corresponding RRs for current smoking. This suggests that any impact of ETS will not have a substantial effect on the estimates of cases saved from these diseases."[12] (Module 6, p. 18)

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